

Human quadriceps strength and fatiguability in patients with post viral fatigue

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Abstract

Quadriceps isometric strength, activation and fatiguability were measured in 11 patients with symptoms of fatigue three months after glandular fever or a glandular fever-like illness. Predicted normal and lower limits of normal muscle strength were calculated from height and age. These measures and the fatigue index were compared with a group of healthy students of similar age. Two of the patients were unable to activate fully their muscles. After allowing for this inhibition the group mean (SD) strength was 104 (22)% of predicted. Although there was no significant difference in the fatigue index between the patients and the control group, there was a trend for the patients to show less fatigue than controls. There was no difference in the muscle results for those patients who were found to have Epstein-Barr virus infections and those who did not. The feelings of weakness and fatigue experienced by the patients could not be explained by either physiological muscle fatigue or lack of effort.

Recently much attention has been focused on the chronic fatigue syndromes, an ill-defined group of conditions including neurasthenia,¹ chronic fatigue syndrome,² effort syndrome,³ Da Costas syndrome,⁴ post-viral fatigue syndrome,⁵ fibromyalgia,⁶ Royal Free disease,⁷ and myalgic encephalomyelitis.⁸ As yet there is no consensus regarding the aetiology of the condition. Common symptoms include persistent fatigue and weakness which are often exacerbated by exercise. Symptoms may last up to several years and, as some of the names suggest, the condition often appears to be triggered by a viral infection. Similar symptoms, such as painful muscles and increased susceptibility to fatigue can occur during acute viral infection.⁹

No difference in muscle isometric strength or fatiguability has been found in patients with "effort syndrome".¹⁰ No reduction in muscle strength has been found in patients with "chronic fatigue syndrome", although an impairment of recovery of maximal isometric strength following endurance testing was found.¹¹ The authors admit, however, that this may have been due to reduced motor neuron recruitment. Byrne and Trounce found normal muscle enzyme concentrations in 11

patients with "chronic asthenia and myalgia of obscure aetiology."¹²

Increased jitter values have been found in some patients by single fibre electromyography¹³ but their physiological significance is uncertain. Arnold *et al* described in one patient with post-viral fatigue an exaggerated early and sustained fall in tissue pH with exercise, as measured by phosphorus nuclear magnetic resonance.¹⁴ However, further work by the same group has shown poor specificity and sensitivity of these muscle abnormalities in "post-viral" fatigue states.¹⁵ Not one of these studies involved groups of patients with corroborated evidence of infection at onset. Doubt remains therefore about the muscle physiology of patients with genuine corroborated post-infectious fatigue.¹⁶

During acute viral and other infections, however, Astrom *et al* found focal deviations in myofibrillar and Z-line organisation and decreased enzyme levels which did not correlate with the severity of myalgia.¹⁷ Similar, although more extensive alterations are often found in a variety of other more specific muscle disorders.¹⁸ Friman⁹ found decreased isometric strength in several muscle groups during acute infection compared with recovery. In a prospective study on the effect of sandfly fever Friman and colleagues found decreased strength during but not after fever.¹⁹ These changes were not accompanied by alterations in the relevant enzymes in serum or muscle nor by altered muscle ultrastructure. The impairment was correlated with the severity of self-reported symptoms, such as myalgia, but not with the severity or duration of fever.

The voluntary testing of maximal strength clearly requires full understanding of the manoeuvre and a high level of motivation. Even when both these requirements are fulfilled the muscle can be inhibited by pain, or fear of pain, from damaged joints or muscle.^{20 21} Weakness may therefore be due to submaximal activation of the muscle rather than muscle atrophy. Only one of the studies on patients with chronic fatigue tested for full muscle activation.¹⁰

Infectious mononucleosis (glandular fever) is a disease anecdotally acknowledged to be associated with delayed convalescence due to fatigue or depression.²² Studies of muscle strength and fatiguability in symptomatic patients after definite viral infection have not been reported. In this study we have tested muscle strength and fatiguability in a group of

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symptomatic patients three months after the onset of a glandular fever-like illness. Using a superimposed electrical stimulation technique we have examined the ability of the patients to fully activate their muscle during the strength testing.

Subjects and methods

Eleven patients were selected from a longitudinal study of 249 patients recovering from an infectious illness.²³ All 11 had attended their general practitioner and had been sent to St Bartholomew's or Hackney Hospitals, London, for a monospot blood test for infectious mononucleosis. Patients were selected consecutively as complaining of significant physical fatigue and fatigability two or more months after a glandular fever-like illness, without suffering from an affective illness. The investigators were unaware of the outcome of the test or diagnosis until the study was complete. A control group of 11 young healthy volunteers was recruited from a group of students. Subjects gave their written informed consent for the study which was passed by the Research Ethics Committees of St Bartholomew's and University College Hospitals.

Patients were tested a mean of three months (range 2–4.5 months) after the onset of the viral illness. The test procedure involved a maximal strength test and fatigue protocol of the quadriceps muscle group. Only the right leg was tested. During the strength test maximum activation of the muscle was checked using superimposed stimulation.

Quadriceps strength was determined during a maximal voluntary isometric contraction (MVC).²⁴ Subjects were seated in an adjustable straight backed chair with the lower leg dependant and the knee held at 90°. The pelvis was restrained with a lap strap and an inextensible strap was looped around the ankle and attached to a strain gauge at the back of the chair. Subjects were asked to extend the knee against the strap with as much force as possible, and the best of three manoeuvres was recorded as the maximum strength.

Maximal activation of the quadriceps during the MVC was tested using a percutaneous twitch superimposition technique.²⁰ This involved percutaneous stimulation of the quadriceps at 1 Hz via pad electrodes. The voltage was set so that approximately 50% of the muscle was stimulated. Two twitches were recorded with the muscle at rest; the subject was then asked to perform a maximal contraction with twitches superimposed. During a truly maximal contraction no extra force is generated by the stimulation on top of the voluntary force. Where extra force is generated by the stimulation the true maximum can be estimated from the height of the extra force relative to the height of the twitch before the voluntary contraction.

Fatigability was tested by repeated isometric contractions of the quadriceps with a target set to 60% of the MVC. The duty

cycle consisted of contractions of 1 second duration with 1 second rest for a total of 20 minutes with the timing controlled by a metronome. Every 5 minutes the subjects performed a maximal effort. At the end of the 20 minutes, or when subjects could no longer maintain the target force, another maximum contraction was performed with superimposed twitches. The fatigue index was expressed as the maximum force achieved after 20 minutes as a percentage of the fresh MVC force.

Patients had serial blood taken for serological testing for antibodies against Epstein-Barr virus, cytomegalovirus, hepatitis A and C, *Toxoplasma gondii*, adenovirus and other relevant pathogens. Patients were given a standardised psychiatric interview before muscle testing.²⁵

The Student's unpaired *t* test was used to compare the patient and control groups and the muscle strength of the patients predicted values.

Results

There were 11 patients (seven female, four male) who had a mean age of 20.9 years (range 16–27) and 11 controls (five female, six male) who had a mean age of 22.5 years (range 20–25). There was no significant difference in sex ratio or age.

The patients varied widely in the amount of time spent in bed and time off work. The mean time in bed was 11 days (range 0–39 days) and the mean time spent off work was 34 days (range 0–87 days).

Seven of the patients had had a primary Epstein-Barr virus infection, one had had hepatitis A. No serological diagnosis was made in the remaining three patients, although all three were recovering from illnesses of glandular fever type, and two had had a positive monospot test and atypical lymphocytosis at onset. There was no difference between the results for strength and fatigability between the patients who had had EBV infections and those who had not. One patient had alcoholism (Research Diagnostic Criteria²⁶) drinking an average of 33 units per week. Ten patients had symptoms consistent with a fatigue syndrome.²⁷ One patient had fatigue as his only symptom. No patient met the criteria for a depressive illness, anxiety disorder, or somatisation disorder.²⁶

In healthy subjects there is a known relationship between height and quadriceps strength.²⁸ For each subject the predicted normal and lower limit of normal (+ 2SD) strength was calculated from height with adjustments for age and sex.^{29,30} All subjects fell within the normal range of strength for their height. All of the control subjects could fully activate their muscles but two of the patients were inhibited. For these two the extra force generated by the twitch was used to calculate the true maximal force of the muscle. As a group the mean (SD) measured strength was 104 (22)% of predicted which is not significantly different from 100% ($p = 0.28$). Using these values the mean measured and predicted strength values for the patients are given in the table.

Table Quadriceps strength (MVC; N, Newtons), predicted strength for height and fatigability for patients with symptoms of fatigue and normal controls. (Fatigue index only includes those subjects who completed the 20 minutes exercise).

	Patients			Controls	
	MVC (N)	Predicted MVC (N)	Fatigue Index (%)	MVC (N)	Fatigue Index (%)
Mean	448	444	77.4	514	69.7
SD	99	111	11.1	113	9.5
n	11	11	9	11	11

The group mean quadriceps strength for the controls was greater, although not significantly so, than in the patient group ($p = 0.08$). This may reflect the greater mean height of the control (1.73 m) compared with the patient (1.70 m) group caused by the larger number of men in the control group.

As the quadriceps are weight bearing muscles, a relationship also exists between body weight and strength.²⁴ The measured strength was 96 (24)% of that predicted for weight which was also not significantly different from 100% ($p = 0.29$).

All of the patients and control subjects found the fatigue test strenuous and required a lot of encouragement. Two of the male patients were unable to complete the full 20 minutes of exercise. The group mean fatigue score for the patients who completed the 20 minutes was 77.4 (11.1)% and for the whole group 73.7 (13.7)%. The mean fatigue score for the controls was 69.7 (9.5)%. Therefore there was a remarkable trend for the patients to show less fatigue than the healthy controls, whether completing the fatigue protocol ($p = 0.06$) or not ($p = 0.2$). It seemed that the control subjects needed greater encouragement in completing the protocol than the patients.

Discussion

We have found normal strength and fatigability in a group of fatigued patients three months following a viral infection, primarily EBV infectious mononucleosis. At the time of testing the patients felt fatigued with limited exercise tolerance. The subjective feeling of fatigue, which is well known following this type of illness, could not be explained by peripheral changes in muscle isometric force generation or fatigability. At the same time, all but two patients were able to generate their predicted maximal strength and showed normal fatigability. Thus we found no evidence that reduced effort has an aetiological role in acute post-viral fatigue for the large majority of patients. No attempt was made to rate the perceived effort during the fatigue test but it appeared to the investigator, rather surprisingly, that the patients found it easier to complete than the controls. Lloyd *et al* found that patients with a chronic fatigue syndrome (duration greater than six months) perceived their muscle effort over 45 minutes exercise as "large or very large", but their perception was not significantly different from healthy controls doing the same muscle work.³¹ However, Riley *et al*³² found that patients with a chronic fatigue syndrome (duration greater than six months)

perceived muscle work as more effort than healthy controls.

Human muscle strength is often discussed as if it were a quantity which is easily defined and measured. However, expression of the strength of a muscle such as the quadriceps, even during a simple movement, is the result of a combination of factors which can be broadly classified as either central or peripheral. Peripheral factors may be thought of as those which determine the intrinsic strength of the individual muscle, such as size and fat content and is the strength that would be measured if the muscle was maximally activated by tetanic stimulation. Central factors include volition and inhibition which affect the activity of the motor neurons.^{20,21} Muscle weakness can therefore result from changes in either central or peripheral factors. It is therefore important to assess central factors when trying to measure the maximal voluntary strength of a muscle. The majority of patients in this study had no central inhibition to force generation; only two being unable to maximally activate their quadriceps. We do not know if this inhibition was due to a lack of understanding of the manoeuvre, altered motivation, pain or a fear of pain from muscle or joints. Most healthy subjects have been found to be able to maximally activate the majority of muscle groups.^{20,33-35} However, motivation may be particularly important during acute infection as subjects may feel unable to exert a maximal effort. The pain and stiffness often felt in joints and muscles during flu-like illnesses may also inhibit muscle contraction. Unfortunately, none of the studies which have measured strength during these acute stages of an illness have looked at muscle activation.

Stokes *et al*¹⁰ also measured quadriceps strength and activation in a different group of patients with "effort syndrome" not necessarily following a viral infection and found essentially the same results as reported here. A few patients were unable to fully activate their muscle and the rest had normal strengths for their body weight. It is of interest that the patients who showed inhibition also stopped a cycle exercise test before their predicted maximal heart rate was reached. They also found no difference in fatigability of the adductor pollicis between the patients and a control group. They suggested that the reduced exercise capacity in this group may be due to a reduced tolerance of effort symptoms rather than an intrinsic muscle weakness.

In our study only one limb was exercised using isometric (static) contractions. This is unlike most movements in everyday life where two limbs are normally working dynamically in a rhythmic fashion, with more than one muscle group exercising. It may be that any exercise limitation will only become apparent when a large muscle mass is involved which places a greater burden on the cardiovascular and respiratory systems. A final reason for not finding significant differences between controls and patients might be a statistical type 2 error, although a larger study might replicate our findings that showed less fatigue in patients.

It is often difficult to know what advice to give to a patient who is suffering from a limited exercise capacity following a viral infection. Rest is important in the acute stages of an infection. If rest is continued too long, however, then a vicious circle can develop in which inactivity leads to a loss of aerobic fitness which will cause a greater feeling of weakness, muscle pain and exercise intolerance.^{27 36 37} Riley *et al*³² have recently shown reduced aerobic work capacity in patients with a more chronic fatigue syndrome. One approach to treatment is therefore a programme of rehabilitation which involves a gradual return to exercise which starts with gentle exercise such as stretching and gradually builds up exercise tolerance.^{27 38} McCain³⁹ showed that such a programme improved fitness and was superior to placebo in relieving symptoms in patients with "fibromyalgia", a condition with many similarities to the chronic fatigue syndrome.²⁷ Furthermore, Repsher and Freehern⁴⁰ showed that a programme of exercise given to patients recovering from infectious hepatitis had no detrimental effect on convalescence. We suggest this may be a successful means of hastening convalescence so long as clinically active signs of infection, such as fever and pharyngitis, are absent. Should symptoms last longer than six months a careful review of all possibly perpetuating factors should be made and other treatable disorders managed.^{27 41}

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